

Case Report

Two cases of anaphylactic shock by methylprednisolone in neuromyelitis optica

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Abstract: Steroid pulse therapy with methylprednisolone (mPSL) succinate ester is the most common treatment for neuromyelitis optica (NMO); no cases of anaphylaxis have been reported to date. Here, we report two cases of anaphylactic shock induced by mPSL pulse therapy in patients with NMO and concurrent systemic lupus erythematosus. Both patients had received several courses of mPSL pulse therapy without any problems previously. Repeated mPSL pulse therapy and comorbid humoral autoimmune disease might increase the risk of anaphylaxis. Corticosteroids without succinate esters should be considered as an alternative therapy to prevent anaphylaxis.

Keywords: Neuromyelitis optica, anaphylactic shock, methylprednisolone, betamethasone, succinate ester

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Neuromyelitis optica (NMO) is characterized by recurrent optic neuritis and transverse myelitis. Steroid pulse therapy with methylprednisolone (mPSL) succinate ester is the most common treatment for the relapse phase of NMO as well as multiple sclerosis (MS). Here we report two cases of anaphylactic shock induced by mPSL pulse therapy in patients with anti-aquaporin-4 antibody-positive NMO who had previously undergone several courses of mPSL pulse therapy for relapses without any problems. Our report offers suggestions about the pathogenesis and risk of anaphylaxis with corticosteroids with succinate esters and highlights the efficacy of therapeutic alternatives involving corticosteroids without succinate esters.

Case reports

The first case involved a 27-year-old woman with a 1-year history of NMO and a 13-year history of systemic lupus erythematosus (SLE). She had been treated with 15 mg/day of PSL and 1 mg/kg/day of azathioprine. To date, she has had five attacks of NMO and/or central nervous system (CNS) lupus. For each episode, she had received mPSL pulse therapy without any serious adverse effects. Subsequently, she developed a new relapse in the cervical spinal cord, for which mPSL pulse therapy was also selected. Seven minutes after mPSL administration began, she suddenly developed anaphylactic shock

with a whole-body urticarial reaction, dyspnea, hypoxia (peripheral oxygen saturation 88%), and hypotension (systolic blood pressure of approximately 70 mmHg). She immediately recovered from anaphylactic shock upon intravenous epinephrine administration.

The second case involved a 29-year-old woman with a 3-year history of NMO and a 22-year history of SLE. She had been treated with 15 mg/day of PSL and 1 mg/kg/day of azathioprine. To date, she has had more than 10 relapses, which have been treated with mPSL pulse therapy without any serious adverse effects. She received mPSL pulse therapy again for a new lesion in the right optic nerve. Ten minutes after mPSL administration began, she had anaphylactic reactions manifested as urticaria in the limbs and hypotension (systolic blood pressure of approximately 90 mmHg) followed by sudden delirium. She immediately recovered from anaphylactic shock upon cessation of mPSL administration.

Intradermal allergy tests for six injectable corticosteroids consisting of mPSL, prednisolone (PSL) succinate ester, hydrocortisone succinate ester (HDC-succinate), hydrocortisone phosphate ester (HDC-phosphate), dexamethasone (DEX), and betamethasone (BMS) revealed that succinate-containing corticosteroids (mPSL, PSL, and HDC-succinate)

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Table 1. The features of the anaphylactic reaction cases by mPSL in MS and NMO.

Reference	Age, sex	Past exposure of mPSL	Diseases	Causative steroid	Alternative steroid
Pryse-Phillips et al. ¹	53, M	–	MS	mPSL ^a	DEX
Van den Berg et al. ²	44, F	+	MS	mPSL ^a	Pretreatment by antihistamine
Clear ³	35, M	+	MS, asthma	mPSL ^b	Pretreatment by antihistamine
Burgdorff et al. ⁴	42, M	+	MS	mPSL ^a	Not shown
Shiga et al. ⁵	25, F	+	MS, atopic dermatitis	mPSL ^a	BMS
Deruaz et al. ⁶	21, F	+	MS	mPSL ^a	DEX
Our case 1	27, F	+	NMO, SLE	mPSL ^a	BMS
Our case 2	29, F	+	NMO, SLE	mPSL ^a	DEX

MS: multiple sclerosis; mPSL: methylprednisolone; DEX: dexamethasone; NMO: neuromyelitis optica; SLE: systemic lupus erythematosus; BMS: betamethasone.

^aConfirmed by intracutaneous test or radio allergosorbent test.

^bIntracutaneous test or radio allergosorbent test were not examined.

induced strong allergic reaction in both patients, but not steroids with phosphate esters (HDC-phosphate, DEX, and BMS). Importantly, both patients recovered from their NMO relapse with an alternative steroid pulse regiment consisting of BMS or DEX without any allergic reactions.

Discussion

This is the first report documenting anaphylaxis in patients with NMO caused by mPSL pulse therapy. Six cases of anaphylaxis in patients with MS caused by mPSL pulse therapy have been reported to date.^{1–6} Interestingly, five of six patients received multiple courses of mPSL pulse therapy before anaphylaxis (Table 1). Sensitization with repeated mPSL treatments has been suggested as a causative mechanism of anaphylaxis.⁷ Our patients have also received repeated courses of mPSL pulse therapy, which may have led to acquired mPSL antigenicity. Previous reports have proposed immunological dysregulation as another risk factor for developing mPSL-induced anaphylaxis. Asthma, renal transplantation, rheumatic disease, hypersensitivity to nonsteroidal anti-inflammatory drugs are examples of immunological dysregulation.⁷ Both patients had SLE in addition to NMO. Such co-existence of humoral autoimmune diseases might have increased susceptibility to developing hypersensitization as previous reports have suggested.⁸ Our observations suggest that the combination of repeated mPSL exposure and concurrent SLE may increase the risk of anaphylaxis from corticosteroids with succinate esters.

The reasons why corticosteroids with succinate esters cause allergic reactions more frequently than those

without succinate esters are not fully elucidated.^{9,10} A previous study proposed that the immunogenic role of succinate esters could be attributed to their greater solubility in water and higher affinity for serum proteins. These properties might change the presentation of the steroid molecule from a hapten to a complete antigen.⁹ Accordingly, corticosteroids without succinate esters seldom cause anaphylactic reactions, even in patients with hypersensitivity against mPSL, although cross-reactivity with DEX or other steroids might underlie a rare cause of hypersensitivity.^{9,10} In fact, mPSL succinate ester was the drug causing anaphylaxis in all reported MS cases, and corticosteroids without succinate esters (i.e. DEX or BMS) were used as alternative drugs (Table 1). In the present cases, intradermal allergy tests strikingly identified succinate-containing corticosteroids as the cause and demonstrated that corticosteroids with phosphate esters were not antigenic. Of clinical importance, our observations suggest that alternative steroid pulse therapies involving corticosteroids with phosphate esters such as DEX and BMS could be safe and effective.

In conclusion, our case report suggests that all NMO patients treated with repeated mPSL pulse therapy, especially patients with comorbid humoral autoimmune diseases known to be frequently associated with NMO, have a higher risk of anaphylaxis caused by mPSL. In such cases, special caution should be exercised when using mPSL. For example, injectable epinephrine should be prepared in advance. Furthermore, alternative steroid pulse therapies consisting of corticosteroids without succinate esters should be selected in patients with a history of anaphylaxis.

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